PHARMACOEPIDEMIOLOGIC AND COST EVALUATION OF ASTHMA MANAGEMENT IN UNIVERSITI SAINS MALAYSIA HEALTH CENTER

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by

ABDALLA GORASHI BASHIR AHMED

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DEDICATION

TO

My beloved late father, mother Fatima, brothers, and sisters.

My darling wife Amani,

my lovely sons Mohamed, Abdul Rehman, Asaad and

my pretty daughters, Eieman and Fatima

Who constantly give me moral support, faith, love, and joy

that energises me to pursue and

accomplish my goals.

Abdalla

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
BA	β_2-agonist
CBA	Cost-Benefit Analysis
CEA	Cost-Effective Analysis
CMA	Cost-Minimization Analysis
COI	Cost of Illness
CUA	Cost Utility Analysis
DDD	Defined daily dose
DID	DDD/1000/ day
DDD/1000/day	Defined daily dose per 1000 inhabitants
DU	Drug Utilization
FEV_1	Forced expiratory volume in one second
GINA	Global Initiative for Asthma
GPs	General practitioners
ICS	Inhaled corticosteroid
KE	Ketotifen
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
PDD	Prescribed daily dose
PEFR	Peak expiratory flow rate
PRN	As needed
Ph E	Pharmacoeconomics
RM	Malaysian Ringgit

SD	Standard deviation
SPSS	Statistical Package for Social Sciences
TH	Theophylline
USM	Universiti Sains Malaysia
UK	United Kingdom
US	United States
US$	United States' dollar
WHO	World Health Organization

PENILAIAN FARMAKOEPIDEMIOLOGI DAN KOS PENGURUSAN PENYAKIT ASMA DI PUSAT KESIHATAN UNIVERSITI SAINS MALAYSIA

ABSTRAK

Asma adalah satu penyakit kronik yang memberi kesan kepada lebih kurang 5 hingga 20% penduduk dunia. Ia menyebabkan morbiditi dan mortaliti yang signifikan, mempengaruhi kualiti hidup dan menyebabkan bebanan ekonomi yang tinggi. Objektif pertama kajian ini adalah untuk menilai aspek farmakoepidemiologi pengurusan penyakit asma dengan menilai corak penggunaan ubat penyakit asma dan keduanya, untuk menganggar kos perubatan langsung penyakit asma di Kampus Induk Universiti Sains Malaysia (USM). Data pesakit luar bagi tahun 2003 dan 2004 dengan preskripsi-preskripsi mereka dikumpulkan secara retrospektif dari rekod perubatan elektronik. Kaedah kajian penggunaan ubat dan kos penyakit digunakan dalam kajian ini. Prosedur statistik inferensial yang digunakan termasuklah ujian-ujian Khi Kuasa Dua, Kruskal-Wallis, Mann-Whitney, Wilcoxon dan Student-t. Paras signifikan yang digunakan adalah 0.05 dengan selang keyakinan 95%. Terdapat seramai 205 orang pesakit asma pada tahun 2003 manakala 237 orang pada tahun 2004. Dapatan kajian menunjukkan kebanyakan pesakit adalah berbangsa Melayu, staf USM dan tangunggan. Kebanyakan pesakit adalah di dalam linkungan umur 1-12 serta 26-45 tahun. Dari segi penggunaan ubat, purata bilangan ubat per preskripsi adalah 2.1 bagi tahun 2003 dan 2.2 bagi tahun 2004. Kajian ini menunjukkan agonis-$\beta_{2,}$ yang penggunannya meningkat secara langsung dengan umur pesakit, adalah ubat yang paling

banyak dipreskripsikan dan digunakan bagi tahun 2003 dan 2004. Ubat kortikosteroid inhalasi (ICS) adalah ubat kedua yang paling kerap dipreskripsikan. Seramai 23% dan 26.6% pesakit asma pada tahun 2003 dan 2004 setiap satu mengambil ICS. Kombinasi ubat yang paling biasa dipreskripsikan adalah agonis-β2 + ICS. Kos min dan median preskripsi pada tahun 2003 ialah RM20.44±12.85 dan RM18.29, manakala pada tahun 2004 kos min ialah RM20.13±13.63 dan median sebanyak RM16.89. Kos preskripsi dan kos ubat-ubatan per pesakit per tahun meningkat dengan umur pesakit. Terdapat perbezaan dalam kos preskripsi berdasarkan kategori pekerjaan dan pegawai perubatan. Kajian ini mendapati penggunaan ubat asma meningkat daripada 1.305 DID pada tahun 2003 kepada 1.514 DID pada tahun 2004. Dari segi kos perubatan langsung, 75% daripada kos tersebut bagi kedua-dua tahun 2003 dan 2004 adalah untuk ubat, manakala peratus kos untuk personel kesihatan adalah 25% daripada jumlah keseluruhan kos perubatan langsung. Ubat asma memakan belanja 90% daripada kos total ubat-ubatan bagi tahun 2003 dan 2004. Merujuk kepada ubat-ubat penyakit asma, agonis-β_2 inhalasi terdiri daripada 61% manakala ICS terdiri 23% daripada kos total ubat-ubat bagi penyakit asma. Jumlah keseluruhan kos perubatan langsung bagi pengurusan asma bagi tahun 2003 adalah RM12,929.17 dan kos per pesakit per tahun adalah RM 63.07. Dalam tahun 2004, jumlah keseluruhan kos perubatan langsung meningkat kepada RM15,475.00 dan kos per pesakit per tahun meningkat kepada RM65.30. Perbandingan data bagi tahun 2003 dan 2004 menjelaskan bahawa tiada perbezaan yang signifikan dari segi profil demografik, corak mempreskripsi, kos purata preskripsi, purata lawatan per pesakit, purata bilangan ubat per perpreskripsi, penggunaan drug per

preskripsi, preskripsi ubat-ubatan per pesakit dan kos langsung per pesakit per tahun.

Kata Kunci: Asma, penggunaan ubat, penilaian kos, Pusat Kesihatan, pesakit luar, farmakoepidemiologi, Universiti Sains Malaysia, universiti.

PHARMACOEPIDEMIOLOGIC AND COST EVALUATION OF ASTHMA MANAGEMENT IN UNIVERSITI SAINS MALAYSIA HEALTH CENTER

ABSTRACT

Asthma is a chronic disease that affects about 5% to 20% of the world's population causing significant morbidity and mortality, affecting the quality of life, and resulting in considerable economic burden. The first objective of the study is to evaluate the pharmacoepidemiology of asthma management by evaluating the pattern of anti-asthma drugs utilization and secondly, to estimate the direct medical costs of asthma in the main campus of Universiti Sains Malaysia. Data of outpatients in 2003 and 2004 with their prescription records were collected retrospectively from electronic medical records. The drug utilization research and cost of illness methods were used in this study. The appropriate inferential statistics used include the Chi-square test, the Kruskal-Wallis test, the Mann-Whitney test, Wilcoxon test, and the student t-test. The significance level was 0.05 with a confidence interval of 95%. There were 205 and 237 asthmatic patients in 2003 and 2004, respectively. The findings from this study showed that the majority of patients were Malays, USM's staff members and dependants. Most of the patients were in the 1-12 and 26-45 age groups. In terms of drugs utilization, the mean drug per prescription was 2.1 in 2003 and 2.2 in 2004. The study showed that β_2-agonists, the use of which increased with age, were the most prescribed and consumed drug in 2003 and 2004. The inhaled corticosteroid (ICS) was the second most frequently prescribed drug. 23.0% and 26.6 % of asthmatic patients in 2003 and 2004

respectively took ICS. The most commonly anti-asthma combination prescribed was β_2-agonist + ICS. The mean and median cost of prescription in 2003 was RM20.44±12.85 and RM18.29, while in 2004, the mean cost was RM20.13±13.63 with a median of RM16.89. The cost of prescriptions and the cost of drugs per patient per year increased with age. There were variations in the cost of prescription with regard to category of patients and prescribers. The study found that the consumption of anti-asthma drugs increased from 1.305 DID in 2003 to 1.514 DID in 2004. In terms of direct medical cost, drugs constituted about 75% of total direct medical costs in 2003 and 2004, while the cost of health personnel constituted 25% of total direct medical costs. Anti-asthma medications accounted for 90% of total drug costs in 2003 and 2004. With regard to anti-asthma drugs, inhaled β_2-agonist accounted for 63% of total anti-asthma drugs cost in 2003 followed by ICS (18%). In 2004, inhaled β_2-agonist accounted for 61% while ICS accounted for 23% of total anti-asthma drug costs. The total direct medical cost of asthma management in 2003 was RM12,929.17 and the cost per patient per year was RM 63.07. In 2004, the total direct medical cost increased to RM15,475.00 and the cost per patient per year increased to RM65.30. A comparison of the data for 2003 and 2004 revealed that there was no significant difference in terms of demographic profile, prescribing patterns, the average cost of prescriptions, the average visit per patient, the average number of drugs per prescription, the consumption of drugs per prescription, the prescription of drugs per patient, and direct cost per patient per year.

Keywords: Asthma, cost evaluation, drug utilization, Health Center, outpatient, pharmacoepidemiology, Universiti Sains Malaysia, university.

CHAPTER 1

INTRODUCTION

1.1 Background

According to Evans (1998) and the National Heart, Lung and Blood Institute (NHLBI) and World Health Organization (WHO) (1995) reports, asthma is a chronic respiratory disease that affects 5-20% of the world population and can cause significant morbidity and mortality. People of all ages especially children are affected by asthma. It can be a severe and sometimes fatal disease (NHLBI and WHO, 1995). Asthma affects the quality of life and leads to considerable restrictions on physical, emotional and social activities. Asthma can be significant burden not only in terms of health care costs, but also in terms of lost productivity and reduced participation in family life (Ungar *et al*., 2000; NHLBI and WHO, 1995). Asthma also interferes with schooling and work, as it can lead to absenteeism among children and lost workdays among adults as well as premature retirement (Clark, 1998).

Evidence suggests that the prevalence of asthma around the world is increasing. This ranges from a 50% increase in New Zealand to a 150% increase in Scotland (Palatine and Sly, 1999). The prevalence of asthma among Malaysian children has been reported to be around 4.9-13.8% (Azizi, 1990; Quah *et al*., 1997). The national prevalence of asthma symptoms in children range widely from 1.6% in Indonesia to 36.8% in UK (Beasley *et al*., 1998). However, in Saudi Arabia, it has been found to be 7% to 10% among school children (AL-Frayh, 1990; AL-Rayes *et al*., 1997). A National Health Interview survey conducted in 1995 in the United States indicated that 15 million

individuals identified themselves as asthmatic, with approximately 5 million being under the age of 20 (Benson and Marrano, 1998). In the United States, asthma was the most common chronic illness in children (Kelly and Kamada, 1998).

The increasing of frequency of the asthma coupled with its under diagnosis, its inadequate, inappropriate treatment and the non-adherence to asthma medication prescriptions are considered to be the major factors for deaths and morbidity among asthmatic patients. In addition, asthma consumes high medical care resources (Ganse *et al.,* 2002; Eason and Markowe, 1987; Suissa *et al*., 2002; Suissa *et al*., 2000; Halterman *et al*., 2000; Barnes, 1994; British Thoracic Association, 1982). Asthma can lead to an increase in the socioeconomic burden of individuals suffering from it, as well as that of their families who share the cost. Society as a whole also bears the burden through the loss of economic productivity when patients are unable to work (de Marco *et al*., 2003; Clark, 1998).

Asthma can be alleviated through appropriate asthma management and prevention. The main approach towards the management of asthma is the use of effective treatments (pharmacologic managements), and avoidance of exposure to allergens and other triggers (non-pharmacologic management) (Busse, 1993; Svedmyr, 1997). In addition, education of both patients and health professionals is the key to the success of every asthma management and prevention efforts (Clark, 1998). Furthermore, an improved adherence to prescriptions of long-term control medications (such as inhaled corticosteroids) can lead to reduced morbidity, mortality, and consumption of health care resources (Neffen *et al*. 2006; Goldman *et al.,* 2000; Momile *et al.,* 1996; Schatz

et *al*., 2003). Additionally, it can also reduce the overuse of quick relief, or PRN (as needed) medications (Gottlieb *et al,* 1995). A study of parent-reported pediatric asthma medications use, noted an excessive reliance on PRN medications coupled with non-adherence to control drug prescriptions (Lozano *et al*., 2003).

Although the superiority of inhaled corticosteroids (ICS) for asthma control has been well established, these drugs used irregularly and underused (Staa, *et al.*, 2003; de Marco *et al*., 2005; Anis *et al.,* 2001). Prescribers often hesitate to prescribe ICS due to a fear of systemic side effects. In contrast, patients usually discontinued the use of ICS due to expectations of immediate symptom relief (Anzueto and Angel, 2000). Under treatment of asthma has been reported as a problem in several European countries and in the United States (Kuar *et al.,* 1998; Bousquet *et al*., 1996; Adams *et al*., 2002).

The economic impact of asthma is increasing, particularly in the second half of the 20th century in some countries, and represents a substantial burden on health care resources in these countries. Health care costs are under pressure in all countries, and decisions about the use of new medicines are not only concerned with safety and tolerability assessments, but also value for money (Barnes *et al.,* 1996). Hence, it is important for professionals, health economists, and planners to work as a team to understand the costs of asthma in order to identify where the burden occurs, to assess the effectiveness of current asthma medications, and to know how to achieve optimal cost effectiveness.

When the economic burden of asthma is considered, the assessment of both direct costs (i.e., cost of providing health services) and indirect costs (i.e.,

the value of the resources lost as a result of illness such as absenteeism from work and other daily activities) must be considered (Stempel, 2003; Barnes *et al*., 1996).

For effective asthma management and rational use of antiasthma drugs, it is important to have information on the previous pattern of the use of these drugs, whether health care professionals and public health officials are acting according to national asthma guidelines in asthma management, how much money was spent on asthma management, and where high expenditure occurs.

1.2 Asthma

Asthma is a chronic inflammatory disease of airways, which causes significant morbidity and mortality if not managed optimally. The disease is associated with a range of symptoms, including cough particularly at night, wheezing, breathing difficulty and chest tightness. These episodes were reversible, either spontaneously or with treatment (NHLBI and WHO, 1995).

1.2.1 Classification of asthma

Asthma is highly variable. It can be intermittent, mild persistent, moderate persistent, and severe persistent. The severity of asthma is determined by an assessment of symptoms, its clinical signs, and through measurements of respiratory function using tests such as peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV_1). The determination of asthma severity is very important in asthma treatment, as drug dosage can be determined based on the nature of the disease. In other words, therapy is

increased (step-up) as the severity of asthma increases and is reduced (step-down) as asthma control is achieved (Global Initiative for Asthma (GINA) and NHLBI, 2005; Bennett and Brown, 2003).

Table 1.1 below shows the classification of asthma severity according to the frequency of its symptoms, and pulmonary function measurement as adapted from National Asthma Education and Prevention Program (NAEPP) (1997).

Table 1.1: Classification of asthma severity according to frequency symptoms, and pulmonary function measurement as adapted from NAEPP (1997).

Asthma severity	**Symptoms**	**Nighttime symptoms**	**Lung function**
Step 4 Severe persistent	*Continual symptoms *Limited physical activity *Frequent exacerbation	Frequent	*FEV_1 or PEF ≤ 60% predicted *PEF variability ≥ 30%
Step 3 Moderate persistent	*Daily symptom *Daily use of inhaled short acting β2-agonist *Exacerbations affect activity *Exacerbations ≥ 2 times a week	≥ 2 times a month	*FEV_1 or PEF > 60%-<80% predicted *PEF variability > 30%
Step 2 Mild persistent	*Symptoms > 2 times a week But <1 time a day *Exacerbations may affect activity	> 2 times a month	*FEV_1 or PEF ≥ 80% predicted *PEF variability < 20%
Step 1 Intermittent	*Symptoms ≤ 2 times a week *Asymptomatic and normal PEF between exacerbations *Exacerbations brief (from a few hours to a few days); intensity may vary	≤ 2 times a month	*FEV_1 or PEF ≥ 80% predicted *PEF variability < 20%

1.2.2 Approach of asthma management

There are a few approaches utilized in the management of asthma. In the following subsections, each of these approaches will be explained in detail. They are:

- Patient and family members education: Patients must be knowledgeable about asthma and its treatments. Patients must learn how to take the prescribed medications correctly, to differentiate between quick relief and long-term preventive medications, to avoid the triggers of asthma, to be aware of the steps to follow if symptoms occur, to follow an asthma management plan, and to seek for medical care in order to prevent serious attacks (Gibson *et al*., 2003).
- Avoidance of exposure to allergens and precipitating factors; a critical component of asthma control is the identification and management of allergens or "triggers" of asthma. This approach is appropriate for extrinsic asthma and may be feasible when it is related to some specific situation, e.g. occupational asthma, but it is less feasible if, it is widespread, e.g. house-dust mites (NHLBI and WHO, 1995).
- Use effective medications; this measure includes the use of medications to reduce bronchial inflammation and hyperactivity, and dilatation of narrowed bronchi (GINA and NHLBI, 2005).

1.2.3 Asthma treatment

An assessment of the disease's severity is crucial in determining the optimal treatment. A wide range of different classes of medication are available for treatment of asthma and the selection of optimal treatment or combinations

of antiasthma medication is essential to ensure that the disease is well controlled. It has been suggested that the current trends toward increased morbidity and mortality associated with asthma may be due to under diagnosis, and under treatment of the disease (Barnes, 1994). In general, the treatment regimens should consist of quick relief medications for all patients, and long-term control medications (anti-inflammatory drugs) for all patients with persistent symptoms i.e., steps 2 through 4 severities (GINA and NHLBI, 2005).

1.2.3.1 Quick relief medications

These medications are used by all asthmatic patients. They are bronchodilator drugs, which relieve bronchospams and improve the symptoms of asthma. They should be used as required rather than regularly. The most common quick relief medications used are the short acting β_2-agonists. In some cases, anticholinergic agents are used. They should be taken as required rather than regularly. They consist of three main groups: β_2-agonists, anticholinergics and theophylline.

1- β_2-agonists

These are the most effective bronchodilators with few side effects when taken by inhalation (NHLBI and WHO, 1995; Bennett and Brown, 2003; Tierney *et al*., 2005). Their main side effects are tremor and tachycardia. The short acting formulations β_2-agonists (inhaled salbutamol and terbutaline) are used for acute exacerbations of asthma in addition to short β_2-agonists tablet or syrup. In contrast, long acting inhaled formulations (salmeterol, and formoterol) are indicated for asthma prevention in combination with corticosteroids.

Sustained release oral formulations β_2-agonists (salbutamol) are also available and may be used by patients who cannot use long acting inhaled β_2-agonists (Tierney *et al*., 2005).

2- Anticholinergics drugs

Inhaled anticholinergics have a slower onset but a longer duration of action. They are frequently combined with β_2-agonists in an urgent care setting. They have very few side effects, as they are poorly absorbed from the lung. The common side effects associated with inhaled anticholinergics are dry mouth, blurred vision, and urinary retention. An example of an inhaled anticholinergic is ipratropium bromide (Kelly and Sorkness, 2005; Walker and Edward, 2003)

3- Methylaxnthines (Theophylline)

The short acting theophylline may be used to treat moderate to severe attacks when high doses of inhaled β_2-agonists, the preferred treatment, are not available (NHLBI and WHO, 1995; Kelly and Sorkness, 2005). The addition of short acting theophylline to inhaled β_2-agonists does not provide any additional bronchodilator effect. On the other hands, long acting (sustained release) theophylline is indicated for asthma maintenance therapy in order to control asthma symptoms and to improve lung function. When inhaled corticosteroids and sodium cromoglycate are not available or are too costly, theophylline can be used as a long-term medication (Aracangello and Peterson, 2006; Tierney *et al*., 2005)

Theophylline appears to exert a weak bronchodilator and/ or an anti-inflammatory effect. These drugs are found in oral and parenteral form and they

have a narrow therapeutic window (Kelly and Sorkness, 2005; Walker and Edward, 2003). At therapeutic serum level, theophylline can cause a variety of cardiac and central nervous system effects including palpitations, tachycardia, tremor, insomnia, headache, and irritability (Tierney *et al*., 2005). Because of its potentially serious side effects, theophylline is usually considered as only a third line agent for asthma management. Its sustained release form is useful in nocturnal asthma (Weinberger and Hendeles, 1983), (e.g. Nuelin SR, Theodur, and Euphylline.)

1.2.3.2 Anti-inflammatory drugs

These drugs are used for patients with persistent asthma and they act by reversing and preventing inflammation caused by an asthma attack. These drugs include:

1- Corticosteroids

Corticosteroids are the main prophylactic drugs in adult asthmatics. They are indicated for both prevention and the treatment of asthma exacerbations. They should be taken in inhalation in minimum doses to reduce their side effects (Toogood, 1990). On the other hand, since an optimal response to ICS requires 4 weeks of therapy, the oral or parenteral routes may be used for severe chronic asthma exacerbation (Kelly and Kamada, 1998). Common oral corticosteroids include prednisolone and methylprednisolone, while examples of ICS include beclomethasone dipropionate, budesonide, and fluticasone. Study estimates suggest that compliance with inhaled corticosteroids is only about 34 to 56% (Yuksel *et al*., 2000). ICS side effects are generally minor. The most

common side effects are dysphonia, cough, and oral candidiasis (Walker and Edward, 2003). These side effects are attributed to oropharyngeal depositions of the drug.

2- Sodium cromoglycate (Intal)

Sodium cromoglycate impairs the immediate response to allergen and acts by inhibiting the release of mediators from the mast cells (Kelly and Sorkness, 2005; Aracangello and Peterson, 2006). Cromoglycate is not effective at terminating an existing attack, i.e. it prevents bronchoconstriction rather than induces bronchodilation. It is administered by inhalation (well absorbed from the lungs, but poorly absorbed from gastrointestinal tract) and is very safe with no significant side effects. It is useful in extrinsic (allergic) and exercise-induced asthma (Bennett and Brown, 2003).

Nedocromil sodium is structurally unrelated to cromoglycate but has a similar profile of actions and can be used by metered aerosol in place of cromoglycate (Bennett and Brown, 2003).

1.2.3.3 Other drugs

Antileukotrienes are bronchodilators that act by terminating the actions of leukotrienes. The NAEPP recommends that the antileukotrienes (zileuton, zafirlukast, and montelukast) should be considered as second or third line drugs for asthma control following β_2-agonists and corticosteroids. Adverse effects of antileukotrienes are infrequent and mild including headache, dizziness, nausea, and diarrhea (GINA and NHLBI, 2005; Tierney *et al*., 2005)

Ketotifen is a histamine H1-receptor blocker and also may have some antiasthma effect, but it has been proven to be of limited efficacy and benefit in many clinical trials. Similarly as with other antihistamines, it can cause drowsiness (Bennett and Brown, 2003).

1.2.3.4 Stepwise approach to therapy and asthma guidelines

The appropriate management of asthma depends on an accurate assessment of asthma severity and the appropriate prescription of medications. In order to establish the proper management parameters, various sets of asthma guidelines, both national and international guidelines such as Global Initiative for Asthma (GINA), and the Malaysian consensus guidelines on the management of asthma (Malaysian Thoracic Society, 1996) have been issued over the last few years. These guidelines have been designed to help primary care physicians, GPs, nurses, public health officials, and program planners in the management of their patients, in order to reduce the personal, social, and economic burden of asthma. Though these asthma guidelines were published ten years ago and emphasize the use of ICS as the first line treatment for persistent asthma, the results of various studies suggested that the health professionals do not strictly adhere to them (Gourgoulianis *et al*., 1998; Vermeire *et al.,* 2002; Poluzzi *et al*., 2002; Verleden and Vuyst, 2002; Donahue *et al*., 2000). Consequently, this problem leads to poor quality of life among patients, and a heavy social burden (de Macro *et al*., 2003).

Despite improvements in understanding asthma pathophysiology and the availability of effective drugs over the last decade, poor asthma control has led to an increase in asthma frequency and severity in many countries, both

among children and adults. There are two major reasons for the lack of success in the management of asthma. First, under prescribing of medications by doctors (Rabe *et al*., 2004; Adams *et al*., 2002; Cydulka *et al*., 2005), and second, the poor prescription compliance by patients (Cerveri *et al*., 1999). Poor compliance of patients can be overcome by patient education, more frequent patient contact, the development of a close patient-clinician partnership, and simplification of treatment (Bender, 2002; Stempel *et al.,* 2005).

Because of variations in asthma severity among different patients, and within each patient over a period of time, a step approach to therapy is recommended to control asthma with the least possible use of medications (GINA and NHLBI, 2005; Tierney *et al*., 2005). The number and frequency of medications increase (step-up) as asthma worsens and decrease (step-down) when asthma is kept under control. After classifying the severity of a patient's asthma, the physician or GPs should judge the treatment stage. Once control is sustained for about 3 months, a reduction in therapy or step-down can be considered. This helps to reduce the risk of side effects and enhances adherence to the treatment plan (NHLBI and WHO, 1995). The National Asthma Education and Prevention Program (NAEPP, 1997) has developed treatment recommendations specific to each severity level (please refer to Table 1.2). Among them are, patients should take a rapid acting bronchodilator, such as a short acting inhaled β_2-agonist, for relieving asthma exacerbations regardless of the disease's severity. Patients with mild intermittent asthma (Step 1) do not need daily maintenance medications since these patients have normal pulmonary function between attacks. However, if these patients are using their β_2-agonists more than twice a week, a step-up in the treatment regimen is

needed. Patients with mild, moderate, and severe persistent asthma (Step 2, 3, and 4, respectively) require daily use of maintenance medications. Maintenance or “preventive” medications include ICS, oral steroids for severe asthma, theophylline, long acting β_2-agonists (salmeterol, formoterol), mast cell stabilizers (cromolyn, nedocromil) and antileucotrienes ((GINA and NHLBI, 2005; Tierney *et al*., 2005; Kelly and Sorkness, 2005).

Table 1.2: Stepwise and approach for managing asthma in adults and children over 5 years of age (Adapted from NAEPP, 1997)

Asthma severity	Long term management	Quick-relief for exacerbation
Persistent-severe Step (4)	Daily medications: *Anti-inflammatory: High dose ICS (500-2000µg/ day or more, beclomethasone equivalent) + *Long acting bronchodilator-either long acting inhaled β_2-agonist, theophylline SR or long acting β_2-agonist + *Corticosteroid tablets or syrup (2mg/ kg/ day, not to exceed 60mg/ day).	Short acting inhaled β_2-gonist on PRN basis
Persistent-moderate Step (3)	Daily medications: Anti-inflammatory: either *Medium dose ICS (500-800µg/day) beclomethasone equivalent or *Low medium dose ICS + *Long acting bronchodilator (long acting inhaled β_2-agonist, theophylline SR or long acting β_2-onist) If needed: *Medium high dose ICS (500-2000µg/day) or beclomethasone equivalent. + *Long acting bronchodilator, specially for night symptoms (long acting inhaled β_2-agonist, theophylline SR or long acting β_2-agonist)	Short acting inhaled β_2-gonist on PRN basis
Persistent-mild Step (2)	Daily medications: Anti-inflammatory: either *Low dose ICS or *Cromolyn or nedocromil (usually chosen as the first line for children) Other alternatives: *Sustained –release theophylline (to serum level of 5 to 15µg/ ml; generally not preferred. *Antileukotrienes may be also considered for patents ≥12 years old; however, the exact place of antileukotrienes in therapy has not been firmly established.	Short acting inhaled β_2-gonist on PRN basis
Intermittent-mild Step (1)	Daily medications: None needed	Short acting inhaled β_2-gonist on PRN basis

1.3 Asthma in Malaysia

A National Health and Morbidity Survey in 1996 indicated that the prevalence of asthma in Malaysia was 4.2%. The survey also shows that the prevalence of asthma varied according to the socioeconomic status of the patients, and the geographical area. The study found that asthma was high among lower socioeconomic groups (low education and income levels), and in rural areas. By ethnicity, Chinese have a lower prevalence of asthma than the other races. In terms of age, the study found that the prevalence of asthma decreased by age but increased again after 40 years and above. The survey finding also revealed that the majority of asthma cases was categorized as mild (87.3%), followed by moderate (9.9%). Only 2.7% of the asthma patients surveyed had severe asthma. The study also found that the majority of mild asthma (65%) and moderate asthma cases (52%) were on non-inhaler treatment. The similar survey revealed that there was inadequate treatment and monitoring of asthmatic patients especially those with severe cases of asthma. This eventually leads to high expenditure in health care costs (Rugayah *et al*., 1999).

1.4 Asthma in the USM Health Center

Data obtained from USM's Health-Care Report indicates that, asthma ranked second after hypertension among chronic diseases in USM's Main Campus in 2001 and 2002 (Izham, 2003). There were 238 asthmatic patients in 2001 and 237 in 2002. Table 1.3 shows the number of patients with different chronic diseases.

Table 1.3: Number of patients visiting the USM Health Center during 2001 and 2002 with different chronic diseases*

Disease	Patients number (2001)	Patients number (2002)	Increase rate (%)
Hypertension	374	449	20.1
Asthma	238	237	-0.4
Diabetes	175	208	18.9
Other (circulatory problem)	39	18	-53.8
Ischemic heart disease	27	40	48.1
TB	7	3	-57.1
Total	860	955	11.0

*Source: USM's Health-Care Report (Izham, 2003)

1.5 Pharmacoepidemiology

In order to choose an appropriate disease management regime and to obtain the rational use of drugs, it is important to have information on the past and present use of drugs. This information must be concerned with types of drugs prescribed, to which patient they were prescribed and indications on their use. In addition, it is important to know the therapeutic cost/ benefit of drug use. This is because without knowledge of how a drug is actually used, it is impossible to discuss what correct or incorrect therapy is, or suggests measures to improve prescribing habits, or initiate a discussion on rational drug use. This information must be made available in drug utilization statistics for the ultimate result. This information will help to assess whether the drug is being rationally used or not (Nordic Council on Medicines, 1990; WHO, 2003). This

can be achieved by applying pharmacoepidemiology methods. WHO defined it as “the study of the clinical use of drugs in populations or the study of the use and effects/ side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population, thereby improving health outcomes” (WHO, 2003).

1.6 Drug Utilization

Drug utilization (DU) is essential part of pharmacoepidemiology and they are some times used interchangeably (WHO, 2003). DU was defined by WHO as “the studies of marketing, distribution, prescribing, and use of drugs in society, with special emphasis on resulting medical, social and economic consequences”. DU can be divided into descriptive and analytical studies. The descriptive studies describe the patterns of drug utilization and identify problems that need more studies, while analytical studies try to link data on drug utilization and figure on morbidity with the outcome of treatments and the quality of care with aims of assessing whether drug therapy is rational or not. The WHO defines the rational use of drug as each patient receiving medication appropriate for their clinical needs, at an optimal dose, for an adequate period, with minimum costs to them and the community.

Drug utilization data provide indispensable information on drug prescription and can be used to:

- describe patterns of the drug’s use
- look at the development of therapeutic profiles
- estimate the number of patients exposed to various drugs

- measure the effects of educational, informative, regulatory efforts, price policies, and reimbursement schemes, etc.
- define areas for further investigations on the efficacy and safety of drug therapy.
- indicate over-use, under-use, misuse, and abuse of drugs.
- estimate drug need in a society (related to morbidity pattern) to be used as a bases for the planning of drug selection, supply, and distribution.

1.6.1 Units of measurement in drug utilization studies

In order to measure drugs use, it is important to have both a classification system and a unit measurement. To study drug use over time, it is important to have a stable and consistent method, which makes it possible to compare drug statistics both nationally and internationally (WHO Collaborating Centre for Drug Statistics Methodology, 2005). There are many different ways of expressing drug consumption (cost, volume measures, prescribed daily dose (PDD), and defined daily dose). None of these measures alone gives a complete picture of drug utilization, but if used in combination, they may serve as data for monitoring purposes.

1.6.1.1 Cost

Drug use can be expressed in terms of costs (e.g. national currency). Cost figures are suitable for an overall cost analysis of drug expenditure. Cost analysis is also applicable for prescription studies of only one substance. National and international comparisons based on cost parameters are often

misleading and are of limited value in the evaluation of drug use. Price differences between alternative preparations and different national cost levels often make evaluation difficult. Long-term studies are also difficult due to fluctuations in currency and prices. When cost data are used, the cheaper drugs may have little effect on the total levels, while the shift effect to more expensive drugs is more readily noticeable (WHO Collaborating Centre for Drug Statistics Methodology, 2005).

1.6.1.2 Volume

Common physical units (e.g. gram, kilos, and liter), number of packages or tablets, and number of prescriptions are used in the calculation of the amount of drugs consumed. If consumption is given in terms of grams of an active ingredient, drugs with a lower potency will have a larger fraction of the total than drugs with a higher potency.

Counting the numbers of tablets also has disadvantages because the strength of the tablets may vary, resulting in outcomes that indicates low strength preparations contribute more than high strength preparations (WHO, 2003). In contrast, the numbers of prescriptions do not give a good expression of total use, unless the total amounts of drugs per prescription are being considered. Counting prescriptions, however, is of great value in measuring the frequency of prescriptions and evaluating the clinical use of drugs (e.g. diagnosis and dosage used) (WHO Collaborating Centre for Drug Statistics Methodology, 2005).

1.6.1.3 Prescribed daily dose

The prescribed daily dose (PDD) is the average daily amount of drugs that are actually prescribed as obtained from a representative sample of prescriptions (WHO Collaborating Centre for Drug Statistics Methodology, 2005). It can be calculated by getting information on the quantity dispensed, the strength and the number of days of supply. PDD should interpreted together with the diagnosis as the recommended dose may differ from one indication to another, or due to the severity of the illness. Furthermore, the dose may differ according to age, sex, as well as local and national therapy traditions. It should be noted that PDDs may differ from one country to another and even between regions or health facilities within the same country. So when making international comparisons this must be in considerations. When there is a substantial discrepancy between the PDD and the defined daily dose (DDD), it is important to consider this discrepancy when evaluating and interpretating drugs consumption figures.

1.6.1.4 Defined daily dose

The defined daily dose (DDD) is a technical unit of drug consumption measurement as assigned by the WHO Collaborating Center for Drug Statistics Methodology (1993). It was developed to work with the Anatomical Therapeutic Chemical (ATC) Classification system in order to overcome objections against traditional units of measurement of drug consumption. The DDD for a given drug is the assumed average maintenance dose per day for a drug used for its main indication in an adult (WHO Collaborating Centre for Drug Statistics Methodology, 2005). DDD does not necessarily reflect the recommended, or

actual dose used, rather it is used as a measurement of drug utilization within, and across drug classes. It is also used when comparing drug utilization studies carried out at different locations and at different time periods. DDD is usually used expressed in DDD per thousand persons per day (DDD/ 1000/ day), and provides a rough estimate of consumption and not a real picture of actual use. For drugs used continuously, the number of DDDs gives a rough estimate of the numbers of its users. The DDD metric may not reflect the recommended or actual used dose (PDDs). Many drugs are for instance used in different dosage on different indications. The PDDs differ between countries, ethnic group and even between area or health facilities within same country. Thus, it can be surmised that prescription data presented in DDDs will only provide a rough estimate of consumption and not a real picture of actual use. The other limitation of the DDD metric is that the DDDs for certain drugs have not been established. Examples of these drugs include preparations for topical use, IV solutions, sera, antineoplastic drugs, general and local anesthetics, and X-ray contrast media (WHO Collaborating Centre for Drug Statistics Methodology, 2005).

1.6.2 Anatomical Therapeutic Chemical Index

The Anatomical Therapeutic Chemical (ATC) Index is an Anatomical Therapeutic Chemical classification system that assigns code letters and numbers to all drugs on an ATC basis (WHO Collaborating Centre for Drug Statistics Methodology, 2003). In the ATC system, the drugs are divided into 14 different groups according to the organ and system on which they act, and their chemical, pharmacological, and main therapeutic use. There is only one ATC

Code for each pharmaceutical formulation and different ATC Codes are given for substances available in two different strengths or for formulations with clearly different uses. This system has been officially adopted by the Nordic countries and the WHO Drug Utilization Research Group (DURG), which has used it for a number of years (WHO, 2003).

No drug classification system is ideal from a combined epidemiological, clinical pharmacological, pharmaceutical, and chemical point of view. A drug may be used for a variety of clinical purposes and drugs of different structures may be used more or less for the same disease or symptom. Accordingly, pragmatic compromise solutions are to a certain extent necessary. Thus, when drug data are related to a specific area of use, reclassification may be helpful before interpretation. The ATC system is suitable for use in both manual and computerized systems. Table 1.4 below shows the ATC Code and the DDD of commonly used antiasthma drugs (Gislason *et al*., 1997).

Table 1.4: Defined daily doses (DDD) of commonly used antiasthma drugs

Drug	ATC code	One DDD per mg	Notes
β2-agonists			
Salbutamol inhaler	R03AC02	0.8	Aerosol/ powder
Terbutaline inhaler	R03AC03	2.0	Aerosol/ powder
Oral salbutamol	R03CC02	12.0	Oral/ parenteral
Oral terbutaline	R03CC03	15.0	Oral/ parenteral
Inhaled steroids			
Beclomethasone inhaler	R03BA01	0.8	Aerosol/ powder
Budesonide inhaler	R03BA02	0.8	Aerosol/ powder
Anticholinergics			
Ipratropium inhaler	R03BB01	0.12	Aerosol/ powder
Oxitropium inhaler	R03BB02	0.6	Aerosol
Theophylline	R03DA04	400	Oral
Cromoglycate inhaler	R03BC01	40.0	Aerosol/ powder
Ketotifen	R06Ax17	2.0	Oral

1.7 Pharmacoeconomics

The rapid growth of health expenditure accompanied with limited resources has led to an increased interest in the economic evaluation of health care interventions. Most health care professionals especially pharmacists, are constantly faced with doing “more with less.” At the same time, they need to satisfy their patients health care demands based on their real needs and on

their wants. So pharmacoeconomics and outcome research must be a part of the background and expertise of many health professionals and pharmacists to enable them to allocate available resources according to priorities and to make choices between different pharmaceutical interventions.

Pharmacoeconomics analysis is defined as a tool to identify, measure, and compare cost and consequences (outcome) of pharmaceutical interventions with the aim of allocating health care resources and of optimizing patient outcomes for a given limited supply of resources (Bootman *et al*., 1991; Drummond *et al*., 1997). Costs are broadly classified as direct, indirect, and intangible costs. While outcomes are broadly categorized into economic, clinical, and humanistic outcomes (Reeder, 1995).

The objectives of pharmacoeconomics are to:

- optimize the patient's outcomes with limited resources.
- help in making critical decisions such as which drug should be in the health care formulary.
- defining the best strategy for managing a particular disease through a creation of clinical guidelines for diagnosis and treatment.
- help the policy maker and administrator to decide which services should be implemented within their organization
- determine how health resources should be allocated
- identify which of the series of alternative therapies will achieve the best cost effectiveness.
- provide valuable information for health care decision makers

The common types of pharmacoeconomics studies are outlined in the following sections: